Move to the homepage, the Leeuwenhoek specimens site, or the introduction to research. See also summary of an earlier presentation.

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Ford, Brian J., 1998, Frühe Mikroskopie, *Spektrum der Wißenshaft:* 68-71, June.

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FROM DILETTANTE TO DILIGENT EXPERIMENTER: A REAPPRAISAL OF LEEUWENHOEK AS MICROSCOPIST AND INVESTIGATOR

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Antony van Leeuwenhoek(1632-1723) remains one of the most imperfectly understood figures in the origins of experimental biology. The popular view is that Leeuwenhoek worked in a manner that was essentially crude and undisciplined,using untried methods of investigation that were lacking in refinement and objectivity. He has often been designated as a "dilettante". His microscopes, furthermore, have been described as primitive and doubt has been expressed over his ability to have made many of the observations attributed to him. Recent research shows these views to be erroneous. His work was carried out conscientiously, and the observations were recorded with painstaking diligence. Though we may see evidence of his globulist understanding of organic matter (and indeed, this view has frequently been cited as evidence of his observational inadequacies), this minor preoccupation cannot detract from two firm principles that underlie his work: (a) a clear ability to construct experimental procedures which were, for their time, rational and repeatable, and (b) a willingness both to fly in the face of received opinion - for example, over the question of spontaneous generation - and to abandon a previously held belief in the light of new evidence.

In his method of analysing a problem, Leeuwenhoek was able to lay many of the ground rules of experimentation and did much to found, not only the science of microscopy, but also the philosophy of biological experimentation.[1] At the time of his entry into the world of observational microscopy, Leeuwenhoek was already following several noted predecessors. We may cite examples:

HUMAN HISTOLOGY

- Capillary circulation in the lung (Malpighi, 1661)
- Hematology and general organ microscopy (Malpighi, 1665-6)

ENTOMOLOGY

- Insect morphology (Power, 1664; Hooke, 1665)
- Anatomy (Swammerdam & Malpighi, 1669)

BOTANY

- Plant Histology (Grew, 1672; Malpighi, 1675, 1679)

EMBRYOLOGY

- *Rana* (Swammerdam, 1669)
- *Gallus* (Malpighi, 1673) [2]

However, it was typical of these earlier workers that they confined themselves largely to microscopical investigation, with some small degree of preparative technique (injection with air, for example, or the dissection of material). Leeuwenhoek assuredly entered the field with purely observational microscopy, too; but in his developing understanding we may perceive the origins of experimental biology. Leeuwenhoek's birthdate might seem to categorise him as a seventeenth century investigator. Had he begun work at twenty years of age and retired at sixty-five, his active years would have been 1652-1697. It is noteworthy that he did not start his microscopical activities until he was forty. On his death bed, aged over ninety, he was still dictating new observations. Thus, his active period covers 1673-1723 and many of his observations set in train the experimental work of the 1700s.

Documentary evidence of Leeuwenhoek's interest in experimentation may be found in the letters in which he recorded his work. The bulk of these were sent to the Royal Society of London, and are preserved in the Society's rooms in Carlton House Terrace. [3] Leeuwenhoek's first letter was sent to Royal Society by de Graaf in 1673. The manuscript is lost. It appeared in *Philosophical Transactions*, VIII (94), 6037-6038 as: A Specimen of some Observations made by a Microscope, contrived by M. Leeuwenhoek in Holland, lately communicated by Dr. Regnerus de Graaf; the illustrations were published later, in VIII (97), 6116-6119. In it he took the unnamed Robert Hooke to task for some of the descriptions published in *Micrographia*, 1665, Martyn and Allestry. It is clear that Leeuwenhoek was much influenced by this tome, which had been a talking-point during his (only) visit to London in 1668. The citing by Leeuwenhoek of the same specimens as those described by Hooke, and in the same numerical order, is a clear indication of the connection. The chances of a random selection of specimens proving to be coincident are worse than 1 1023, given the possible number of species from which material could be selected. The argument that Leeuwenhoek had been told the kind of material of interest to the Fellows of the Royal Society is not convincing, either; even here the chances are remote that the three Leeuwenhoek would elect to send would be identical with those categorised by Robert Hooke - and in the same order of listing.

Within a short time, Leeuwenhoek was beginning - not merely to observe - but to experiment. His earliest examples of specimen preparation date from the letter of 1 June 1674. Here he prepared fine sections of elder pith, and cork, and enclosed these in a folded envelope for the Secretary of the Society, Henry Oldenburg, and his 'curious friends' to observe. [4] By 7 September 1674 he was working on the anatomy of the eye through dissection, and on 4 December of that year he described work on the optic nerve (specimens of which I have found still survive, and were amongst those described elsewhere, *supra*. The drawing sent with the letter of 26 December 1674 is preserved at the British Museum under Additional Sloane MSs folio 125, and the letter with which the specimens of optic nerve were sent to London was dated 22 January 1675. Thus, within less than two years of starting work, Leeuwenhoek was sensing the need to evolve technical methods in his research, and was beginning to move towards practical experimentation. Leeuwenhoek was elected to Fellowship of the Royal Society on the strength of his pioneering investigations. He was not alone in being so honoured, though a foreigner: Giovanni Domenico Cassini,Christiaan Huygens, G. W. Leibnitz, Marcello Malpighi and Vincenzo Viviani came into the same category.

What marked out Leeuwenhoek was his determination to work independently. There had been nothing in his background to suggest any form of philosophical training or educational specialisation. His parents had been Phillip - a maker of the wicker baskets used to transport the fine wares produced in Delft - and a brewer's daughter, Margaretha. Following the death of his father the young Leeuwenhoek was sent away to be educated and in due course he was apprenticed to a cloth merchant. The young Jan Swammerdam was in Amsterdam at the same time as Leeuwenhoek was serving his time in that prosperous town, though we could not deduce that there was any cross-fertilization of ideas. Leeuwenhoek was sixteen, whilst Swammerdam was only eleven. Neither should we be too easily persuaded that Leeuwenhoek's interests in lenses arose from the cloth counters - lenses used to measure the density of warp and weft in the textiles which he graded - since there is no evidence that Leeuwenhoek became interested until he was intrigued by Hooke's already published descriptions. The accounts from 1673 describe Leeuwenhoek's microscopes as being of recent invention, furthermore.

Once qualified, Leeuwenhoek went to work for a Scottish trader, William Davidson, who dealt with the East Anglian textile merchants. At the age of 22, Leeuwenhoek returned to Delft and purchased a house, The Golden Head, in which he lived for the remainder of his life. Leeuwenhoek's mother died in 1664, his own wife Barbara died in 1666, and it was in this same year that he took on the job of Chamberlain of the Council Chamber. This honour, somewhat akin to being 'master of the king's bedchamber', as Elmer Bendiner has fittingly said [5] offered him a degree of civic status and a permanent source of income. With this (and the inheritance from his mother's estate) he was able to concentrate on his investigations. His marriage in 1671 to Cornelia Swalmius (daughter of a merchant who dealt in serge, and a distant relative of his first wife Barbara) brought him into contact with a more intellectual group and within two years he had embarked on his life's work as a microscopist.

I have elsewhere drawn attention to the distinction that should be drawn between Leeuwenhoek's microscopical investigations and those of his contemporaries. They, typified by Robert Hooke, were concerned with the magnification of the already-familiar: fleas and lice, nettles and bee stings.But Leeuwenhoek was concerned with the previously invisible and unsuspected: the globules in milk, erythrocytes in the bloodstream, and microbiota of ponds, lakes and streams. Though he was not (as Bendiner sensibly emphasised in the title of his paper) the inventor of the microscope, he was the father of high-power microscopy and the progenitor of microbiology. Little attention need be paid to the oft-repeated argument that Leeuwenhoek was unable to read English, since he was a self-confessed monoglot speaker of the Early Modern Dutch of his time. As modern workers know very well, it is always possible to find some friendly individual able to render into one's mother tongue a publication written in a foreign language, and Leeuwenhoek was known to consult translators when he needed them. In his letters he cited works published by philosophers who did not communicate in Dutch; they included Willis's *CerebriAnatome* (1645), the 1665/7 *Micrographia* of Hooke (to which allusion has been made earlier), Swammerdam's *Historia Insectorum Generalis* of 1669, Redi's influential *Experimentacirca Generationem Insectorum* (1671), de Graaf's *De Mulierum Organis Generationi* (1672), Grew's *Comparative Anatomy of Trunks* (1675), and Willoughby's *Historia Piscium* of 1686. His knowledge of many of his contemporaries was considerable, and his lack of ability to translate was manifestly no insurmountable obstacle to his desire to know what others were publishing.

Let us examine how this links Leeuwenhoek with eighteenth-century experimental biology. An examination of the status of his investigations as that century begins sets his work in a clearly forward-looking context. He begins his eighteenth-century work with a letter written to Sir Hans Sloane in London and dated 2 January 1700. In it, Leeuwenhoek describes the colonial flagellate *Volvox*. He reveals the delicacy of structure, the crystalline beauty of the organism, and its characteristic method of locomotion, rolling through the aquatic environment, propelled by the coordinated beating of cilia of the daughter-cells. But he then moves on to evolve an experimental rationale that enables him to study the reproductive mechanisms of this colonial organism. He selects two of the colonies and traps them in a narrow glass tube. One end of the tube he closed with cork, leaving a region of air between the cork and the column of water. Even before Leeuwenhoek examines the organisms which are the centre of this study, he is writing observations on the system he has thus created: "One cannot approach the tube with the hand, the breath, or any other part of the body that is a little warmer than the air now shut inside the tube, without the air being affected by some part of it ... even though we may perceive no motion with the naked eye".From this colloquial account of a primitive thermometric mechanism Leeuwenhoek moves on to describe in detail the behaviour of the volvocine colonies he has separated from the rest of the culture. As he expected, small daughter-colonies were released from within each of the mature spheres of cells. He continued his observations by writing a daily diary of the progression of these newly-released colonies towards full maturity. In this we may see his preoccupation with the defeat of a concept of spontaneous generation; to Leeuwenhoek it always seemed obvious that microbial organisms must have parents, rather than being derived from inorganic matter, and in many of his later experiments he produces evidence in support of his sensible contention. During this work he recorded that the rotifera in the aquatic samples from which he had obtained his *Volvox* colonies contained "red material in their guts" and he related this, correctly, to the free-living *Hematococcus* which he studied at some length. In noting that the red coloration of the rotifera was derived from their consumption of the free-swimming red algae, Leeuwenhoek recorded that "some of these animals ... had none of the red material in them, particularly the young ones which had not long left their mothers' body".

He also studied *Chlamydomonas*, a green coloured free-swimming organism, and here inoculated cultures into samples of water that were free of such contaminants. His accounts show that he transferred the cells to both fresh and boiled water: do we here see an anticipation of the "vital force" concept of later years? On Christmas Day 1702 Leeuwenhoek made his discovery of the sessile ciliate *Vorticella*, "fashioned like a bell, and at the round opening (making) such a stir that particles in the water thereabouts were set in motion ..." Leeuwenhoek, it should be noted, considered himself a poor draughtsman and utilized the services of a limner to assist in recording his observations. His account of rotifera adds: "Suddenly there came out its roundness two little wheels, which displayed a swift rotation. The draughtsman, seeing the wheels go round and round, and always turning in the same direction, could not have enough of looking at them, exclaiming, 'Oh, that one could ever depict so wonderful a motion'!". During these observations Leeuwenhoek also recorded *Hydra* [6] for the first time. During these years Leeuwenhoek witnessed the apparent ability of certain aquatic organisms (notably the rotifera) to survive periods of dessication. In his letter to the Society dated 5 November 1716 he wrote of a culture he had left dry "for a whole winter" and recorded that: "when I put some of them in water I saw them unfold their limbs, which seemed to be wrapped up inside them, and swim about." It was also in 1700 that Leeuwenhoek successfully undertook an experiment on the parasitism of aphids. Endoparasitic organisms were viewed by Leeuwenhoek's contemporaries as examples of the mysterious workings of a creator [7] and it is noteworthy that, although Redi had by this time shown that dipteran species were not produced spontaneously, even he was not drawn to a universal view that all life arose from living progenitors (clearly the opinion of Leeuwenhoek at this time). In 1678 Leeuwenhoek noted the apparent emergence of a fly (Cole assumes this to have been a hymenopteran parasite) from the cocoon of a caterpillar. Eight years later he set up experiments to isolate insects emerging from the galls of oak and thistle, and began the study of galls of willow. He showed that in the first two cases, the larva of the insects (*Cynipsfolii* and *Urophoras cardui* respectively) caused the trauma to the host plant from which eventuated the gall itself. Though he noted the development of the larva and pupa within the gall mass, he did not complete the life-cycle of either species. By 1695 he had watched the hatching of Chalcid parasites from the apple ermine moth *Hyponomeuta*, and during the same period he was first acquainted with parasitism in the aphids. His observations were stimulated first by the observation of some empty exoskeletal structures of aphids, each punctured by a neatly bored hole (through which, as he rightly surmised, the parasite had emerged). He went on to examine a number of turgid and immobile aphids in which he found the entire body cavity was taken up by a larva. His first conclusion was that a female 'ant' had laid eggs which hatched to produce the voracious maggots he observed. By 1696 he had shown that the apple sawfly *Hoplocampa* was the origin of larvae found inside those fruit, and that the parasite now known as *Therioaphis* may be hatched from infested specimens of *Tilia*, the lime. In 1700 he succeeded in demonstrating the completion of the cycle, through observation of the breeding behaviour in adult parasites. His use of a confined chamber for the isolation of his specimens enabled him to observe the hatching of flies from the bodies of parasitised aphids. Of fundamental importance was his subsequent observation of oviposition, and he clearly noted the fact that copulation in these flies did not precede the egg-laying phase. He went further, and confined adult newly-hatched parasitic flies with lepidopteran caterpillars, noting that the parasites could not be induced to lay eggs on the (alien) host species. He wrote that the ovipositor was produced "in the manner of a sting" and was used to inject the eggs into the host. During the following year he observed two parasites within a willow gall, and showed that the smaller larva was parasitic upon the larger. His descriptions of the organisms and their microscopical structure are accurate to a degree; he was able to demonstrate experimentally that the smaller larva feeds upon the larger, and that both mature to form disparate species. His work on parasitic mechanisms laid the firm foundations for this previously unexplored area of biology, and the experimental techniques which he utilized launched parasitology as a philosophical discipline.

During the late 1690s, Leeuwenhoek advanced the view that the annular structures observed on fish scales corresponded to the age of the fish in years. By 1716 he was diverted by the common carp, *Cyprinus*, and required a means of examining the layering configuration in greater detail. To do this he evolved the technique of sectioning the scales at an angle, thus exaggerating the apparent thickness of the separate layers. His experimental approach involved soaking the scales in water for long enough to soften the structure, and then cutting sections at an extremely oblique angle.

Similar techniques have been used in the succeeding centuries to clarify laminar structures, and one modern application is the forensic analysis of multi-layered painted surfaces. Leeuwenhoek was rightly fascinated by image-forming structures apart from lenses. In 1674 he had reported producing an image using, as a lens, the ovum of a cod. Twenty years later he generated clear images of a candle-flame through the compound corneal structures of the dragonfly *Libellula*. By 1700 he had reported on the optical arrangement of the centipede *Scolopendra* and wisely concluded that the compound eye he painstakingly dissected did not provide multiple images, any more than a human has double vision through the possession of two eyes. He used his ability in microdissection to examine the ommatidia of *Crangon*,the common shrimp, and dissected out the crystalline cones using a hand-held needle. That most entrancing of microscopical subjects, *Daphnia*, came to his attention in the same year. Leeuwenhoek had carried out extensive studies on blood circulation during the seventeenth century, and now recognised that the contractile vescicle he observed in the thorax of the water-flea was its heart. His earlier descriptions of erythrocytes frequently alluded to their being composed of smaller globules. Possibly he had observed cells undergoing crenation, in which rounded projections appear to form on the surface of each cell as the cytoplasmic volume decreases. His observations of the blood cellsof the flounder include the crucial comment that each ovoid cell contained a clear central zone. This, through the work of Robert Brown in the 1820s, proved to be the cell nucleus [8].He seems to have repeatedly concluded that erythrocytes were discoid or oval, yet returns time and time again to a globulist view - and at one stage during 1700 he proposed that human erythrocytes might be composed of 36 globules (six component spheres each comprising six sub-units). He even produced wax spheres which he packed together and described in detail, in an attempt to support this globalist proposition. The fact that his experimental procedures did not offer the confirmation he sought did not, at the time, deter him from continuing this largely groundless speculation. The detailed examinations he made in that year ranged from the newt *Triton* to the lizard *Lacerta*; it covered a range of fish and even the spider *Araneus*. By1708 he had experimentally removed the living heart from a small eel, *Anguilla*, and maintained it beating for four hours*in vitro*. His skill at microdissection also enabled him in 1700to dissect from the queen honey-bee *Apis* a vast number of immature eggs, and to show that the 'king' bee, as it was then known, was no 'king' at all, but a queen.

The most compelling version of Leeuwenhoek's introduction to the microscopical universe is contained in the compelling biography of Clifford Dobell, whose widow Monica has broadened and deepened my understanding of the published account [9]. Leeuwenhoek described microorganisms including algae, protozoa, rotifera and bacteria in fresh water samples and recorded that: "The motion of most of them in the water was so swift, and so various, upwards, downwards, and roundabout, that I admit I could not but wonder at it. I judge that some of these little creatures were above a thousand times smaller than the smallest ones which I have hitherto seen on the rind of cheese, wheaten flour, mold and the like". Similarly, from his letter on pepper-water described by R. T. Gunter's *Early Science in Oxford*,(1931) **VIII**, 299: "Some of these are so exceedingly small that millions of millions might be contained in a single drop of water. I was much surprised at this wonderful spectacle, having never seen any living creature comparable to those for smallness; nor could I indeed imagine that nature had afforded instances of so exceedingly minute animal proportions". Yet he remained intrigued by the conventional behaviour of more familiar species. On 12 October 1685 he wrote on his observations of seeds. His description of the cassia seed causes him to consider an experimental means of confirming his observational conclusions:

"As regards the cassia seed, I find in it the beginning of a plant; that is, chiefly the leaves, which, I trust, have been made so exceedingly large in order to provide nourishment for that part of the root and for the beginning of the young plant; which root, by comparison with the two leaves, is very short. In order to satisfy myself on this point, I have laid the cassia seed to sprout in sand moistened with common rain-water, until the root had grown as long as the width of my thumb, when the two aforesaid leaves had been pushed outside the earth, having between them the beginning of the young plant, which before that could not be discerned."

He adopts an innovative approach for the examination of the internal structures of the cotton seed, a topic addressed in his latter of 2 April 1686:

"I have thought fit to put some cotton seeds - which I have had by me for over a year, and which are so old that their greenish colour has already faded - in water for one night, after which I removed from them their tough rind, being their first; and then their soft membrane, being their second envelope; and separated the leaves a little from one another. Eight or nine of these seeds, from which the young cotton tree takes its origin, I send you herewith. On these a sharp eye will recognise, even without any magnifying lens, not only the four distinct leaves, together with that part which will become the root and stem; but one will also be able to see the small spots on the leaves [10]." He derived a clearer view of the internal structure of these seeds by the use of a technique latterly known as serial sectioning. Leeuwenhoek took some of the soaked cotton seeds and "cut one of them into twenty-five to twenty-six round slices, and the other into twenty-eight to twenty-nine round slices, which too I send you herewith."

The *Collected Letters* published a footnote to this (Volume VI p 11) to the effect that the 'slide' Leeuwenhoek sent to the Royal Society is "no longer in the library". At the time, a 'slide' would not, of course, have existed; and the correspondent was equally wrong to imagine that the material was missing. The translations were done from microfilm copies of the original letters, and the small packets which Leeuwenhoek had used to contain his specimens were pasted adjacent to his signature. As I have explained earlier, vide: *Notes and Recorded of the Royal Society*, (1981), **36** (1), 37-59, the packets were present all the while, but the image they presented to the camera deluded the translator into thinking Leeuwenhoek had drawn 'rectangles' at the end of his account. The images were, in fact, the outlines of the folded paper packets, unopened for three centuries. The use of the term 'slices' draws a neat distinction between these portions of plant material and the fine sections which Leeuwenhoek had earlier prepared of cork and elder pith, q.v. and his decision to introduce the concept of the serial technique has had many later examples in the realm of experimental biology. Leeuwenhoek may be credited with the establishment of a pioneering example of forensic microscopy. At the time of his active period it was believed that 'heavenly paper' descended from time to time to the earth's surface, as though messages from a divine source. The charred appearance of the samples almost suggests an early anticipation of the heat of re-entry! Some small fragments were collected by one of Leeuwenhoek's correspondents in Courland on the Baltic coast. They took the form of blackened fragments of a papery substance and were safely contained in a square of paper folded over four times.(An identical method of enveloping has come down to the present time in the field of gemmology, for such folded containers are used to hold precious stones during transportation). The handwriting on the envelope suggests that the correspondent was not accustomed to writing in Dutch, and was possibly unfamiliar with the Latin alphabet. Leeuwenhoek examined the specimens when they arrived at his home in Delft. In the letter dated17 October 1687 he wrote:

"I had not had this supposed paper in my house for half an hour before I had (with the aid of the microscope) formed such a clear impression of it, that I concluded it was a plant which had come forth from the water. And moreover, I took it for sure that, if it were true that it had fallen from the sky onto the field, then this substance must first have been driven up into the air(by a cloud which we call a whirlwind). But I much prefer to believe that, due to heavy rains or melting snow . . . the water from a marsh or from ditches had flooded some piece of land, and that the water had left this green plant, from which the supposed paper is made, behind on a greensward or a field with young corn, with the result that the sun and wind caused the plant to become dry and stiff, so that it took on to some extent the look of burned paper."

The original specimen packet was sent by Leeuwenhoek to London with this letter, and indeed the 'heavenly paper' was seventh of the nine specimen packets which I found hidden amongst his correspondence. It should be clearly stated that the appearance of the fragments was that of charred paper; and when a small portion was gold sputtered and examined under the scanning electron microscope the first impression was that of a paper sample. A technician whose previous experience had been in the paper manufacturing industry offered this as an immediate diagnosis on seeing a low-magnification scanning image of the material. Leeuwenhoek's abilities as a microscopical analyst are here thrown into clear perspective: he was making a judgement which might compare favourably with routine forensic examination today. And in this case too, the investigation led Leeuwenhoek to an experimental modelling of the processes which had produced the 'paper'.

His conclusion was clearly that the 'plant' material, as he designated it, had originated as a mass of algal growth floating in water. He emphasises this in the following extract from the letter of 17 October 1687:

"I concluded that I had often seen this substance in large quantities in stagnant waters, such as ditches and excavated ground; but what puzzled me was how I could possibly make this Substance, or green plant, turn into a blackened mass. This green plant is often called felt, but more often slime, by the common person."

From this he proceeded to elaborate a simple technique for demonstrating the production of 'paper' from the slimy growth of chlorophyte algae. His first impulse was to go out of Delft to the drains which abounded in the low-lying lands, but he soon realised he had an alternative supply nearer at hand, and available as a result of the Dutch expertise at managing water flow. The letter continues:

"I bethought myself to go to some swampy fields, situated not far from our City; but on reflection that the canals which run around our City have sluice-gates in two distinct places, in order that the daily current of water should run, not around, but through the City, I went to where the water in the City canal had least movement, and where I saw the slime in abundance. [11] Of this slime I have taken some and laid it on several pieces of thick paper, and dried the same in front of the fire; and I saw that where it lay very thick, it changed by itself from a clear green into a blackish substance; and where it was quite thin it retained its green colour. Furthermore, I once again examined the so-called burnt paper, and now I saw very distinctly that it was one and the same substance, and of the same composition. For, when I examined the green substance, just as I had taken it from the water, through an ordinary microscope, I imagined seeing that these very thin, thread-like parts, which by far exceed a hair in thinness, were round, and that their membrane was very transparent, and that they were filled with green globules . .".

His account adds that he observed 'joints' in the filaments. These were the transverse septa which divide one cell from the next inline. Subsequently Leeuwenhoek collected a further sample of algal material from a barrel of water kept to irrigate a small garden in Delft, and dried it down in a similar fashion before the fire. In this case, he wrote, the papery sample which resulted retained its green coloration. Of this material, and the papery specimen produced in the experiment described above, he sent samples to the Royal Society. The packets were among those I found to have survived intact, and both were made available for microscopical examination. Here we have an anticipation of conventional experimentation. Leeuwenhoek first utilizes his microscope to correctly diagnose the specimen material: it is not the paper it appears, but, rather, a sample of dried algal growth. He then moves on to recreate the original conditions which he postulates gave rise to the specimen. Deciding at first to employ algal material from fields like those in which the original material had been found, he decides instead to opt for more readily-available material in the City canal system. He successfully imitates the process which had been postulated to produce the result observed. And thirdly, he moves on to a separate source of material and repeats the procedure. His first experiment produces a dark-coloured papery specimen; the second produces a 'paper' which is green in colour but otherwise similar. By way of confirmation we see him comparing the results with correlated observations of the original sample. The methodology is empirically developed; it comes close to anticipation of the controlled experimentation employed in more recent times. Investigations of the material have shown how accurately Leeuwenhoek obtained results and interpreted his findings. Interestingly, the fact that he dried down freshly gathered aquatic algal matter implied that - incidentally - he was bequeathing to a twentieth-century microscopist dehydrated samples of the very material which he studied during his microscopical research. Careful reconstitution of the dried material has restored many of the organisms to a near life-like appearance, and has enabled us, for the first time, to identify in Leeuwenhoek's own material some of the aquatic types he described in his letters.

Leeuwenhoek has been described as possibly the first person to prepare sections for the microscope. That clearly cannot have been the case; Hooke portrayed fine cork sections in his *Micrographia* and this was work undertaken a decade before Leeuwenhoek's entrance upon the stage. However, he continued to apply his techniques to an unprecedented range of specimens. In the field of histology he demonstrated, in 1706, the fibrous capsule of the spleen and its trabeculae, pulp and corpuscular structure. He studied striated (voluntary) muscle, the structure of the eye and even (in 1720) sections of bone. Here too he introduced experimental methods, for in 1714 he referred to the transparency of muscle tissue and found how to stain the fibres with a solution of saffron in brandy.

In 1688 he had made his crucial observations of the capillary circulation in the tail of the tadpole stage of *Rana*; by 1700 he was able to document the phenomenon of blood coagulation. During the eighteenth century, Leeuwenhoek undertook accomplished dissections of insect, crustacean and mammalian specimens. For example, he employed microdissection in his studies of the cochineal bug *Coccus cacti*, in which he demonstrated pre-formed insects within egg pouches removed from adult females. He carried out experiments on fumigation with sulphur dioxide, which he produced by burning flowers of sulphur. When moths reappeared in a warehouse he had treated, he rightly concluded they had emerged from chrysalids which - because of their structure - had resisted the effects of the gas; he therefore evolved a scheme to ensure that a follow-up treatment was timed to destroy these. He observed the detonation of gunpowder, compromising his eyesight as he did so, and diligently recorded the effects of aromatic substances as insect repellents and pesticides. His single-mindedness meant that Leeuwenhoek - who showed endless patience with his microscopic subjects - was less concerned with social niceties.

Though visited by Queen Mary of England and the Czar of all the Russias, Peter the Great, he often had distinguished visitors turned away if they had not made an appointment and he felt disinclined to socialize that day. He never read a research paper, taught a student, nor visited a University. Not only was he disinclined to teach, but wrote that he was unwilling to be challenged on his findings. He has been taken to task for a failure to associate microorganisms with the generation of infectious disease, but in my view this assures him of a reputation for far-sightedness. Our microbial compatriots have been viewed for too long as agencies, primarily, of disease; a better understanding of their role is to view them as the seat of environmental regulation, the source of the complex mechanisms which provide our food and our atmosphere, and as objects of incomparable complexity and considerable enchantment. If we were to abandon the view that 'microbes' were synonymous with 'germ', and that 'germ' implied 'disease', I believe science could develop a fuller understanding of the complex interactions which manifest themselves as life. In a primitive way, but with remarkable prescience, Leeuwenhoek was sensitive to this cause. His delight in making new observations, in piecing together new levels of biological understanding, have given him a unique role in the formation of a scientific approach at the very dawn of the discipline.

There remained an attitude that Leeuwenhoek was an outsider, a notion stemming in part from what has been described as intellectuals turning "against Leeuwenhoek". [12] But Leeuwenhoek's abilities are clear from the documentary record and, latterly, are extended by our new knowledge of the exemplary specimens he prepared in the later seventeenth century. He should not be seen merely as an observational microscopist, for his work as an experimenter, allied to his unequalled dexterity as a section cutter and a dissector of minute organisms, give him additional status as a pioneer of eighteenth century experimental biology.

REFERENCES

1: A summary of earlier attitudes towards Leeuwenhoek's working methods appeared in Ford, Brian J., The van Leeuwenhoek Specimens, *Notes and Records of the Royal Society*, (1981) **36** (1), 37-59. The review published as Folkes, M., Some Account of Mr Leeuwenhoek's Curious Microscopes, lately Presented to theRoyal Society, *Philosophical Transactions*, (1724) **32,**446-453, implies - even its title - some degree of condescention. L. M. Becking dismisses Leeuwenhoek as "immortal dilettante" in *Science Monthly,* New York, (1924), **18**, 547; and J. Sachs (1875) regarded him as inconsequential in his *History of Botany*, London & Munich.

2: Modified, after Rupert Hall, Antony van Leeuwenhoek 1632-1723 (The Leeuwenhoek Lecture), *Notes and Records of the Royal Society*, (1989), **43**(2), 249-273.

3: Transcriptions of the letters to the Society, and to Leeuwenhoek's othercorrespondents, are found in *The Collected Letters of Antony van Leeuwenhoek*, *Allede Brieven van Antoni van Leeuwenhoek*, Uitgegeven ... door een Commissie van Nederlandschegeleeren), Swets & Zeitlinger, Amsterdam, 1939-present. It is anticipated that the considerable volume of correspondence will be published in English and Dutch by the end of the twentieth century. It may be noteworthy that the time taken for the publication of the correspondence is a decade longer than it took Leeuwenhoek to originate it.

4: It has been widely believed that all Leeuwenhoek's original materials were lost, indeed the survey by Bracegirdle published prior to this revelation stated emphatically that "no preparations from the seventeenth century had survived." The account (in B. Bracegirdle, 1978, *A History of Microtechnique*, Ithaca: Cornell), adds that any such specimens would have been poorly prepared in any event, and unlikely to reveal much of microscopical interest. However, the discovery that nine specimen packets had survived amongst Leeuwenhoek's correspondence has proved to disclose that he was an excellent microtomist. An analysis of the material is in press, Brian J. Ford, *The Leeuwenhoek Legacy*, Farrand and Biopress, London, 1991 and an early appraisal was published in 1981 as *Notes and Records of the Royal Society*, **36** (1), 37- 59. Brief notes may be found in *Nature*, 1981, **292,** 407 and *New Scientist*, 1981, **91**, 301.

5: An informal account of Leeuwenhoek's early days was published by Elmer Bendiner, The Man who did not invent the Microscope, *Hospital Practice*, August 1984, **139,** 144-160,165-174.

6: Henry Baker reproduced Leeuwenhoek's account of this coelenterate in his *Microscope made Easy of* 1743. His figure III p 94 is a reproduction of the figure 3 in Leeuwenhoek's account, published in *Philosophical Transactions* No 283, 1703. Interestingly, Leeuwenhoek's original submission had shown a diagram of *Hydra* with eight tentacles, increased by the engraver to nine in *Philosophical Transactions*, q.v. This was corrected to eight in the Baker version, strongly suggesting that he referred, not to the published version but to Leeuwenhoek's original correspondence in drawing up his account.

7: The *Deus et machina* of spontaneous generation was examined in the comprehensive paper of F. J. Cole (1937), Leeuwenhoek's Zoological Researches (Part 1), *Annals of Science,* **2** (1), 1-46. Leeuwenhoek's work on the rotifera is summarized in author's *Microscopy,* (1982) **34** (2), 362-373.

8: Brown's coinage of the term is examined in Brian J. Ford, *Single Lens the story of the Simple Microscope,* (1985) Harrap, London; Harper and Row, New York.

9: Clifford Dobell,(1932) *Antony van Leeuwenhoek and his "Little Animals",* John Bale, Sons and Danielsson, London; reprinted by Dover, New York, 1958.

10: Leeuwenhoek's "outer layer" is the seed coat proper; the soft membrane is the endosperm which surrounds the embryo itself. Leeuwenhoek is wrong to refer here to "four distinct leaves", however. Within the cotton seed are two cotyledons. These are folded against each other and are liable to break unless handled with extreme care. It is probable that his manipulations separated the convoluted structures into four separate parts. His description of "small spots" is an example of acutely accurate observational microscopy; these are the glandular structures on the leaves which contain brown or violet secretions.

11: The term Leeuwenhoek used in his letter is *Vlijm*, closest perhaps to 'phlegm' in English. Note too that Leeuwenhoek described the conditioning of the City water courses by means of sluice gates in the letter of 9 October 1676, *Collected,Letters* ... **II**, 85. 12. This view is examined by P. van der Star in: Intellectuals Against Leeuwenhoek, (in) *Antoni van Leeuwenhoek,* eds: L Palm and H Snelders, Amsterdam, 1981.
